REMARKS

Claim Rejections - 35 USC §103

Claims 1, 3-5, 7-12, 14-18, and 21 were rejected under 35 U.S.C. § 103(a) as allegedly rendered unpatentable by Newton et al (U.S. Patent No. 5,595,890) in view of Reynolds et al (U.S. Patent 5,763,184) and Krausa et al. (<u>Human Immunology</u>, <u>44</u>:35-42, 1995). Applicants traverse.

It is respectfully submitted that a prima facie case under 35 USC §103 has not been established. Reynold's statement that the "polymorphic site hybridizes at or near the 3' end of the primer" (column 11, lines 11-14) is inconsistent with Newton. Someone of ordinary skill in the art at the time of the claimed invention would have noted, as the Examiner has, that Newton only teaches the use of the 3' terminal nucleotide as the diagnostic nucleotide. Newton teaches those skilled in the art that the reason for utilizing the 3' terminal nucleotide as the diagnostic nucleotide is for purposes of differentiating those samples containing the target single nucleotide polymorphism ("SNP") from those samples that do not contain the target SNP, because:

"where there is a mismatch between ... the 3' terminal end of the diagnostic primer and the corresponding nucleoside triphosphate in the sample nucleic acid no primer extension will be effected. Where, however, the 3' terminal nucleoside triphosphate is complementary with the corresponding nucleoside triphosphate in the sample nucleic acid, primer extensions will be effected [i.e., primer extension occurs normally]" (column 7, line 64-column 8, line 3)(emphasis added).

Reynolds also states that the effects of primer mismatches are described in a number of cited articles which were incorporated by reference (column 11, lines 11-20). One of the cited references, Kwok et al., 1990, *Nucleic Acids Research* 18:999-1005, teaches away from the claimed invention. In particular, Kwok states in his abstract:

"We investigated the effects of various primer-template mismatches on DNA amplification of an HIV-1 gag region by the polymerase chain reaction (PCR). Single internal mismatches had no significant effect on PCR product yield [i.e., primer extension occurs normally] while those at the 3' terminal base had varied effects." (emphasis added)

Kwok further states on page 1003, first column:

"In the process of generating templates with altered bases, we demonstrated that a single mismatch 3 residues from the 3' terminal base of a primer can be efficiently extended without modification of amplification reaction conditions. Similarly, mismatches 1, 2, or 3 bases from the 3' nucleotide of primer had no apparent affect on overall PCR product yield.[i.e., primer extension occurs normally]" (emphasis added)

Therefore, Reynold's statement that "the polymorphic site hybridizes at or near the 3' end of the primer" is not only inconsistent with Newton but contradicted by Reynold's own cited references. Indeed, Reynold's statement is unsubstantiated with any experimental data. The actual working examples of Reynolds do not utilize an amplification method with a diagnostic primer and, hence, do not offer any practical teaching relating to such a method to one of ordinary skill in the art at the time of the invention. On the other hand, Kwok is an article from a peer reviewed journal which describes actual experiments which demonstrate that a diagnostic nucleotide near the 3' end has no effect on product yield. Accordingly, it is respectfully submitted that Newton and the art cited by Reynolds to support his "at or near the 3' end" statement teaches away from the present invention.

It is well settled that it is impermissible hindsight to pick and choose prior art references in order to create a prima facie case of obviousness. Because the very art cited by Reynolds, i.e. Kwok, as well as Newton, cited by the Examiner, teaches away from the presently claimed method, there was no motivation to combine Reynolds with Newton nor Krausa. Indeed, the unexpected success of the present invention is set forth in Examples 2, 3 and 4.

Claim 6 was rejected under 35 U.S.C §103(a) as allegedly rendered unpatentable by Newton et al. in view of Reynolds et al and Krausa et al, and further in view of Mullis et al. (U.S. Patent No. 4,683,195).

The combination of Newton et al., Reynolds et al, and Krausa et al. do not teach or suggest the claimed invention as discussed above, and the secondary reference Mullis et al adds

no further teachings which would enable one of ordinary skill in the art to achieve the claimed invention.

Claim 13 has been rejected under 35 U.S.C §103(a) as allegedly rendered unpatentable by Newton et al. in view of Reynolds et al and Krausa et al, and further in view of Guatelli et al (Proc. Natl. Acad. Sci. USA, 87:1874-1878, 1990).

For the same reasons provided above, Applicants respectfully submit that none of the cited art teach or suggest the claimed invention and Guatelli et al. is a secondary reference that adds no further teachings which would enable one of ordinary skill to achieve the claimed invention.

Claims 19 and 20 were rejected under 35 U.S.C §103(a).as allegedly rendered unpatentable by Newton et al. in view of Reynolds et al and Krausa et al and further in view of Chen et al (Nucleic Acids Research, 25(2): 347-353, 1997).

For the same reasons provided above, Applicants respectfully submit that none of the cited art teach or suggest the claimed invention, and Chen et al. is a secondary reference that adds no further teachings which would enable one of ordinary skill to achieve the claimed invention.

Claim 22 was rejected under 35 U.S.C §103(a) as allegedly rendered unpatentable by Newton et al. in view of Reynolds et al and Krausa et al, and further in view of Walker et al. (Nucleic Acids Research, 20(7): 1691-1696, 1992).

For the same reasons provided above, Applicants respectfully submit that none of the cited art teach or suggest the claimed invention, and Walker et al. is a secondary reference that adds no further teachings which would enable one of ordinary skill in the art to achieve the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the present rejections under Section 103.

Conclusions

The claims of the present application are believed to be in condition for allowance, and early notice thereof is respectfully requested.

Respectfully submitted,

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